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BRIEF COMMUNICATION

Neuroimaging and electroencephalographic changes after vagus nerve stimulation in a boy with medically intractable myoclonic astatic epilepsy



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Myoclonic astatic epilepsy (MAE) is characterized by multiple seizure types, which are often refractory. Although vagus nerve stimulation (VNS) is an alternative treatment for medically intractable seizures, its exact mechanism of action remains unclear. Herein, we report the case of a 4-year-old boy with intractable MAE who has been in a seizure-free status for 2 years and 3 months since 6 months after the implantation of a vagus nerve stimulator (Model 103, Cyberonics, Inc., Houston, TX). Various test results 6 months after VNS were compared with those before VNS. Results of an electroencephalograph revealed disappearance of epileptiform discharges and an increased beta–gamma spectrum rhythm. The brain diffusion-tensor imaging showed an increased ratio of fraction anisotropy in the right fimbria–fornix, indicating improved diffusion of the white matter tract, and ¹⁸F-fluorodeoxyglucose positron emission tomography revealed globally improved cerebral glucose metabolism. His cognitive and

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social–emotional performances also improved at 2 years after VNS. To the best of our knowledge, this is the first report to describe the effects of VNS on fimbria– fornix and glucose metabolism in MAE.

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Introduction

Myoclonic astatic epilepsy (MAE), also known as Dooze syndrome, is a generalized epileptic syndrome of young children characterized by multiple seizure types, predominantly myoclonic, astatic, and myoclonic astatic seizures, as well as by generalized tonic–clonic seizures, absence, myoclonic absence, and tonic seizures.¹ It should be differentiated from Dravet syndrome (severe myoclonic epilepsy of infancy), which begins with febrile seizure in infants, subsequently evolving into myoclonic seizure and partial epilepsy. Drop attacks predominate in cases of MAE, which are different from the tonic seizures frequently reported in the Lennox–Gastaut syndrome.² In cases of MAE, electroencephalography (EEG) is characterized by a biparietal theta background rhythm, irregularly generalized spike wave, and polyspike-wave discharges. Before the onset of epilepsy, children are developmentally normal and organic brain abnormalities are absent. The victims may become neurologically regressed if the seizures are intractable. However, little is known about the optimal treatment of MAE and the efficacy of antiepileptic treatments has not been studied in randomized clinical trials.³

Vagus nerve stimulation (VNS) is an alternative treatment for patients with medically refractory epilepsy, who are unsuitable candidates for conventional epilepsy surgery. It remains the only nonexperimental surgical option available for patients who need surgical management but are reluctant to undergo an intracranial procedure.⁴ The vagus nerve has a mixed composition with 80% afferent fibers, which originate in the jugular and nodose ganglia and innervate the nucleus of tractus solitarius bilaterally, sending projections to various regions associated with seizure activity.⁵ By stimulating these afferent fibers, VNS attempts to remotely exert its antiseizure effects on intracranial structures. However, the mechanism of these effects remains unclear.

We herein report the case of a 4-year-old boy with medically intractable MAE who became seizure free after undergoing VNS treatment. The changes in EEG and neuroimaging after VNS, including brain magnetic resonance imaging (MRI) and positron emission tomography (PET), are described.

Case report

A 4-year-old boy, the first child of unrelated parents, was uneventfully delivered by elective cesarean section at 38 weeks of gestation. His growth and development were normal until 2 years of age when myoclonic jerks before sleep were noted by his parents. His generalized myoclonic

jerks became worse with shoulder shrugs and brief loss of consciousness (for seconds) 3 months later. There were no obvious precipitating factors. He was treated with valproic acid initially, but in vain. Multiple antiepileptic drugs had then been tried without benefits, including nitrazepam, levetiracetam, clonazepam, topiramate, vigabatrin, lamotrigine, and oral steroids. He still had more than 50 myoclonic jerks, followed by atonic drops with brief absence seizures daily. He was then referred to our hospital. Initially, intravenous pyridoxal phosphate (30 mg/kg) was administered with partial response, which reduced the number of seizures from 70 to 40 per day. A 24-hour video EEG showed frequent bursts of symmetric generalized polyspike waves (Fig. 1A). Results of a brain MRI scan showed no specific finding. An interictal ¹⁸F-fluorodeoxyglucose PET (¹⁸F-FDG PET) study was carried out and the images revealed diffuse hypometabolism at the bilateral frontal, parietal, and temporal lobes (Fig. 3A). Statistical parametric mapping (SPM; SPM99, Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London, London, UK) analysis that compared our patient with 10 healthy young men (age: mean = 33.5 ± 6.0; range = 20–39) as controls⁶ (Fig. 3B, with a height threshold of $p < 0.001$ and extent-size threshold of >90 voxels) showed statistically significant hypometabolism in the marked areas.

MAE was suspected. Adrenocorticotrophic hormones were given for 5 days, but discontinued due to increased number of seizures up to more than 90 per day. The patient was then followed up at our neurologic clinic under the treatment of pyridoxine, valproic acid, lamotrigine and clonazepam, with 10–40 drop attacks per day. Global regression in motor, speech, cognition, and behavior was noted after frequent seizures. He became very hyperactive, wheelchair dependent and incommunicable, lacked verbal output, and required a helmet to avoid head trauma.

He received a vagus nerve stimulator implantation (Model 103, Cyberonics, Inc., Houston, TX) at 4 years of age. Three months after VNS, his major seizures with drops disappeared, although 7–15 absence seizures persisted daily. He became more communicable and started to have social smiles 5 months after VNS. No more seizures were noted and the EEG showed diffuse beta or gamma spectrum fast activities (Fig. 1B) without epileptiform discharges 6 months after VNS.

Compared with baseline (Fig. 2A), the fractional anisotropy (FA) map from brain diffusion tensor image (DTI) at 10 months after VNS showed increased FA in the right fimbria–fornix at the level of both cerebral peduncles (Fig. 2B). Another PET study during VNS, which was performed at 1 year and 3 months after vagus nerve stimulator implantation, revealed global improvement of glucose metabolism in the cerebrum and cerebellum (Fig. 3C: axial images; Fig. 3D: SPM

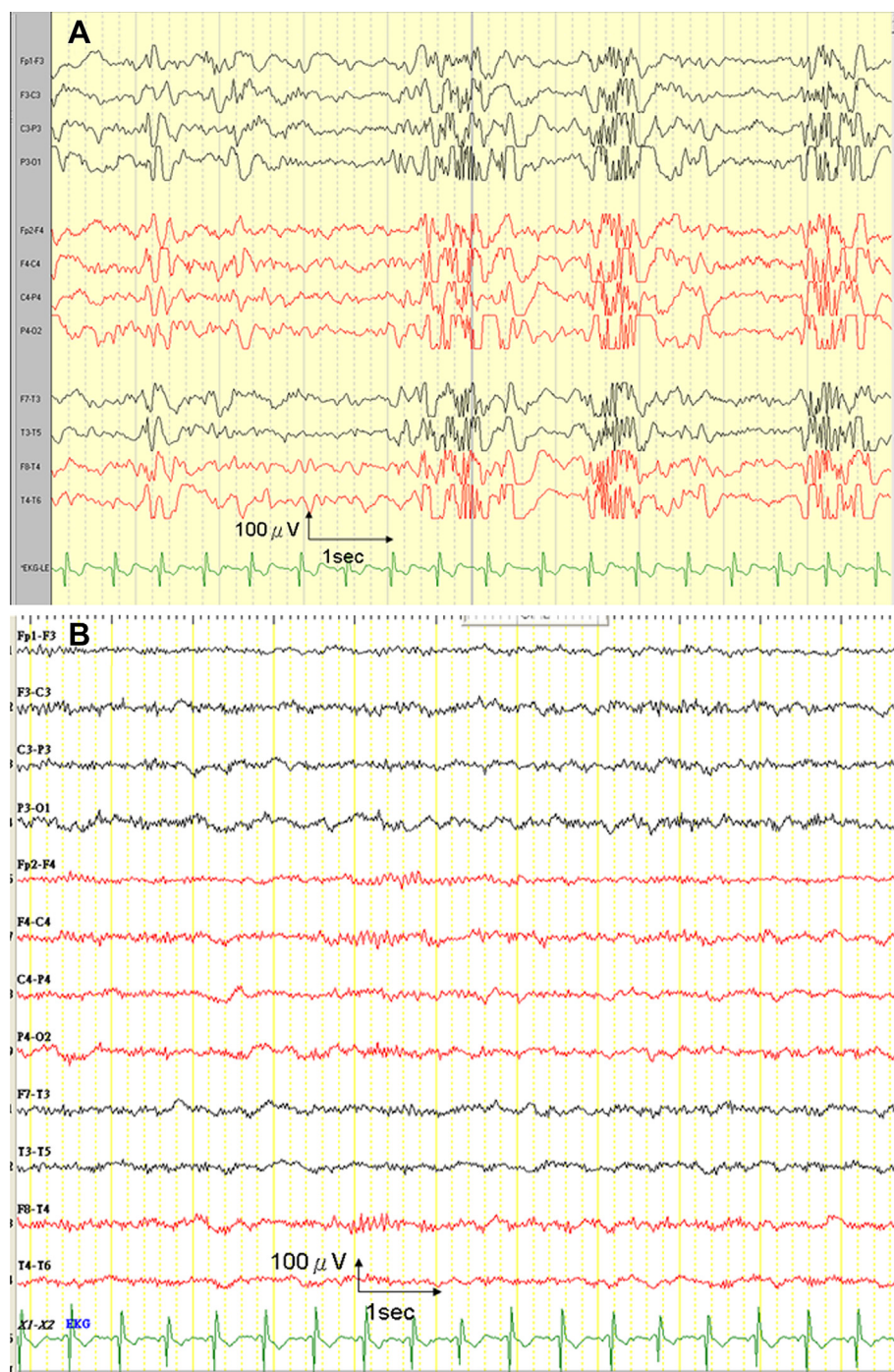


Figure 1 Electroencephalography (EEG) of the patient with myoclonic astatic epilepsy before and after vagus nerve stimulation (VNS). (A) Pre-VNS interictal EEG reveals symmetrical polyspike-wave discharges. (B) Post-VNS EEG at 6 months shows disappearance of epileptiform discharges and increase in diffuse fast activities (high cut set at 35 Hz).

analysis with a height threshold of $p < 0.001$ and extent-size threshold of >90 voxels). Slight asymmetric uptake was noted in the thalamus; the maximal standard uptake value (SUV_{max}) of the right thalamus is 6.6, while that of the left thalamus is 6.1. The psychosocial evaluation by Bayley-III at 2 years after VNS showed significant improvement of raw scores from 41 (equivalent to 12 months old) to 63 (equivalent to 24 months old) in cognitive performance and from 81 to 103 in social-emotional performance; however, there was

no improvement in language performance (raw scores from 47 to 43).

We started to taper his antiepileptic drugs at 1 year after VNS. Treatment with clonazepam had been discontinued, valproic acid tapered to 7 mg/kg per day, and lamotrigine therapy maintained at 7 mg/kg per day. He remains in seizure-free status for more than 2 years, walks and runs independently, plays with peers, and follows orders. He started to be verbally expressive recently.

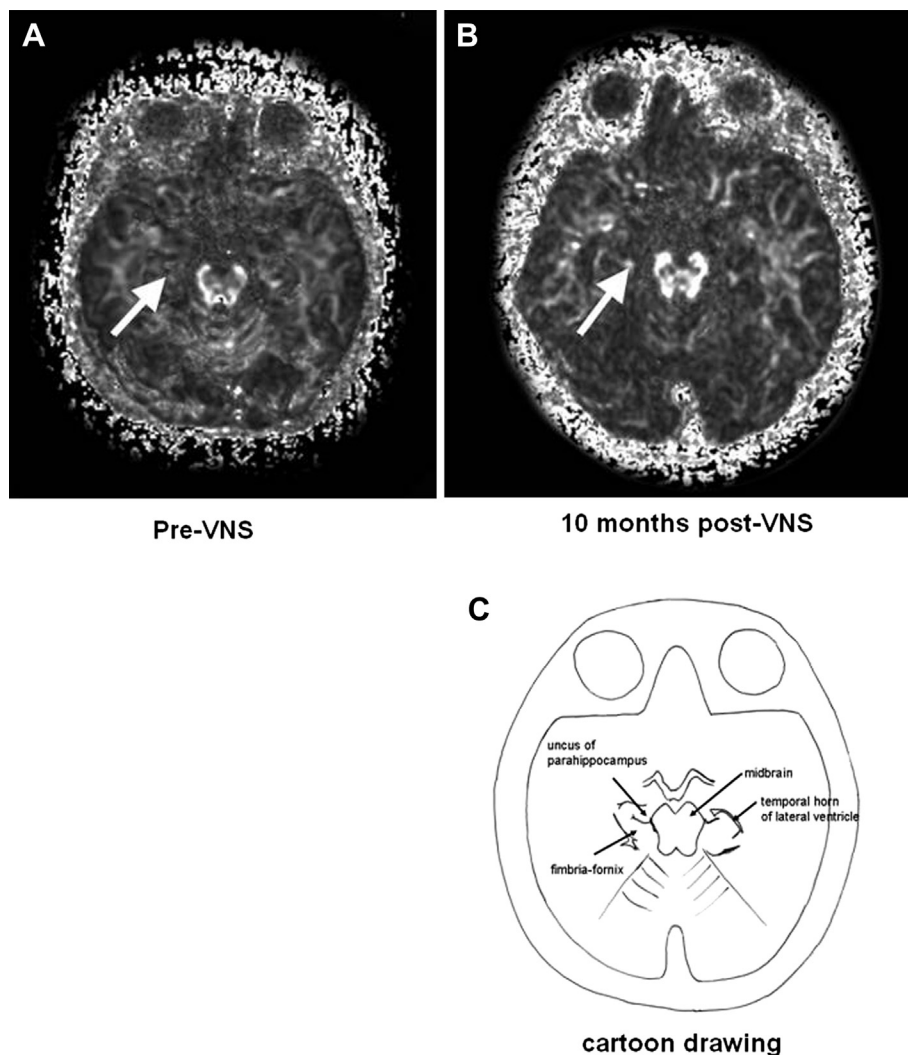


Figure 2 Brain magnetic resonance imaging before and after vagus nerve stimulation (VNS). (A) Pre-VNS diffusion tensor imaging shows decreased fraction anisotropy in the right fimbria–fornix (arrows). (B) Diffusion tensor imaging performed 10 months after VNS shows improvement in the corresponding area. (C) The cartoon drawing demonstrates the location of fimbria–fornix with their corresponding axial fractional anisotropy (FA) maps (A,B).

Discussion

To the best of our knowledge, this is the first report to describe the effects of VNS on the fornix and cerebral glucose metabolism in a patient with MAE.

VNS, usually through the left vagus nerve, was able to increase activity, measured by neuronal *fos* expression, in known vagal projection pathways, e.g., the medullary vagal complex, locus coeruleus, several thalamic and hypothalamic nuclei, amygdala, and the cingulate and retrosplenial cortex.⁷ It was demonstrated to evoke potentials in the cortex, thalamus, hypothalamus, and amygdala of cats and monkeys.^{8,9} *In vivo* DTI, reported to accurately predict white matter abnormalities of the fimbria–fornix in human temporal lobe epilepsy, provides significant validation of the application of DTI as a noninvasive marker of white matter pathology in seizure patients.¹⁰ The baseline cerebral DTI of this patient showed decreased anisotropic diffusion of white matter in the right fimbria–fornix, which

was improved after the seizures were controlled by VNS. The fornix is a bidirectional pathway from the hippocampus, through the hypothalamus to the mammillary bodies and the anterior nuclei of thalamus, which are the target locations affected by VNS. Therefore, the fornix may be involved, while seizures are refractory and later improved after VNS. It is interesting to note that the ¹⁸F-FDG uptake in the right thalamus is also slightly higher than the uptake in the left thalamus after VNS in this patient.

¹⁸F-FDG PET, based on glucose utilization of brain, may provide information on the level of neuronal function in the brain. It has been used in presurgical identification of epileptic foci for pediatric patients with intractable seizure.^{11–15} The interpretation of PET images in the clinical setting is mostly based on visual interpretation. Objective voxel-based analysis technique, such as SPM, is not widely used in pediatric epileptic patients, mainly due to lack of an age-matched control database. It has been demonstrated by ¹⁸F-FDG PET that absolute cerebral glucose metabolic values

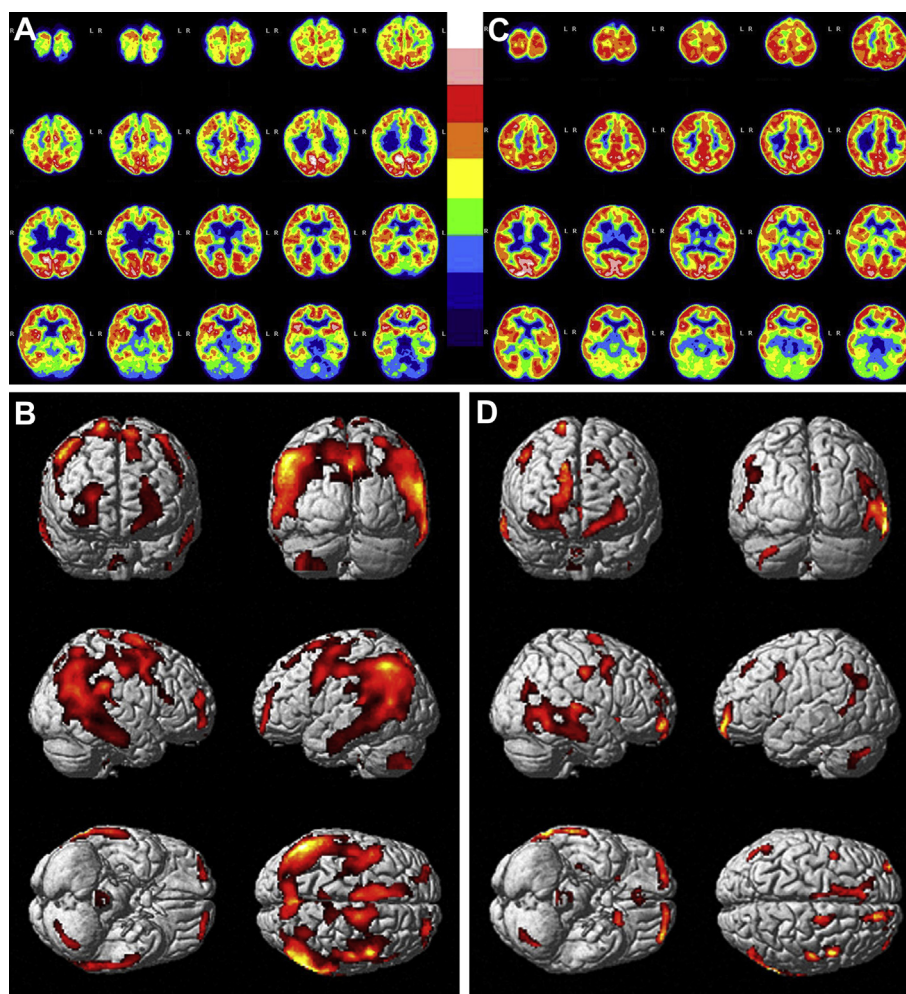


Figure 3 ¹⁸F-Fluorodeoxyglucose positron emission tomography (FDG-PET) studies before and after vagus nerve stimulation (VNS) (A) Pre-VNS PET showing extensive FDG hypometabolism at the bilateral frontal, parietal, and temporal cortex; (B) statistical parametric mapping (SPM) analysis of pre-VNS PET ($p < 0.001$, voxel size > 90 , uncorrected for multiple comparisons) with 10 young men (range: 20–39 years) as controls showing extensive significant hypometabolism at the bilateral frontal, bilateral temporal, bilateral parietal, and left cerebellar regions; (C) PET study performed at 1 year and 3 months after VNS shows global improvement of FDG metabolism. Note that the FDG uptake in the right thalamus is slightly higher than the uptake in the left thalamus; (D) SPM analysis of post-VNS PET using the same criteria and normal database.

for various gray matter regions were low at birth and rapidly rose to reach adult values by 2 years of age.¹⁶ Recently, SPM analysis, using a young adult control group, was shown to be a complementary objective analytic method in identifying epileptogenic regions in children older than 6 years.⁶ We applied a similar method to the PET study performed at 3 years and 7 months of age in our patient. The PET results of diffuse pattern of multifocal hypometabolism are consistent with his EEG findings, and therefore surgery was not a recommended treatment option.

It has been proposed that VNS produces an effective decrease in seizure frequency mainly by suppressing the activity of ipsilateral thalamus. Perfusion studies using ^{99m}Tc-ethylcysteinate dimer single photon emission computed tomography (SPECT) demonstrate significant decrease of perfusion in the left thalamus at VNS initialization.^{17,18} An animal study using ¹⁸F-FDG PET demonstrated decreased glucose metabolism in the left hippocampus immediately after VNS and decreased left-to-right ratio in

the striatum after 1 week of continuous VNS.¹⁹ Consistent with the findings of previous reports, we found lower ¹⁸F-FDG uptake in the left thalamus during chronic VNS in our patient. In addition, we also demonstrate a global increase in the cerebral glucose metabolism, which may be related to the seizure-free status of this patient.

Electrical stimulation of vagus nerve causes desynchronization of neuronal activity in cats and humans,²⁰ which is thought as one of the mechanisms of antiepileptic action. Desynchronization may play a role in regulation or generation of seizures—such as the amygdala, the limbic cortex, and parts of the thalamus—and those that are anatomically connected with the vagus nerve.^{21–23} In animal studies, the 30-Hz (high frequency) VNS setting suppresses interictal epileptiform discharges.²⁴ In addition, EEG beta activity (13–35 Hz) is considered as an index of central alertness.²⁵ Taken together, the increase in beta or gamma spectrum fast activities (20–50 Hz) by VNS, claimed to account for improved attentional performance

and anticonvulsant action,²⁶ potentially explains the improvement in our patient.

In summary, VNS may be an effective treatment for MAE. We hypothesize that the antiseizure effects of VNS in the treatment of MAE may be related to the improvement of cerebral glucose metabolism and white matter diffusion in the fornix, which connects the hippocampus and the thalamus. The latter may mediate cortical desynchronization, presenting as the increase in the beta–gamma spectrum rhythm, which accounts for the anticonvulsant action and improvement in cognitive performance.

References

1. Dooze H. Myoclonic-astatic epilepsy. *Epilepsy Res Suppl* 1992; 6:163–8.
2. Scheffer IE, Berkovic SF. Genetics of epilepsy. In: Swaiman FS, Ashwal S, Ferriero DM, editors. *Pediatric neurology: principle and practice*. 4th ed., vol. 1. Philadelphia: Mosby Elsevier; 2006. p. 1012–3.
3. Kilaru S, Bergqvist AG. Current treatment of myoclonic astatic epilepsy: clinical experience at the Children's Hospital of Philadelphia. *Epilepsia* 2007;48:1703–7.
4. Milby AH, Halpern CH, Baltuch GH. Vagus nerve stimulation in the treatment of refractory epilepsy. *Neurotherapeutics* 2009; 6:228–37.
5. Henry TR. Therapeutic mechanisms of vagus nerve stimulation. *Neurology* 2002;59:S3–14.
6. Kumar A, Juhász C, Asano E, Sood S, Muzik O, Chugani HT. Objective detection of epileptic foci by ¹⁸F-FDG PET in children undergoing epilepsy surgery. *J Nucl Med* 2010;51:1901–7.
7. Naritoku DK, Terry WJ, Helfert RH. Regional induction of fos immunoreactivity in the brain by anticonvulsant stimulation of the vagus nerve. *Epilepsy Res* 1995;22:53–62.
8. Juhász G, Détéri L, Kukorelli T. Effects of hypnogenic vagal stimulation on thalamic neuronal activity in cats. *Brain Res Bull* 1985;15:437–41.
9. O'Brien JH, Pimpaneau A, Albe-Fessard D. Evoked cortical responses to vagal, laryngeal and facial afferents in monkeys under chloralose anaesthesia. *Electroencephalogr Clin Neurophysiol* 1971;31:7–20.
10. Concha L, Livy DJ, Beaulieu C, Wheatley BM, Gross DW. *In vivo* diffusion tensor imaging and histopathology of the fimbria–fornix in temporal lobe epilepsy. *J Neurosci* 2010;30:996–1002.
11. Sood S, Chugani HT. Functional neuroimaging in the preoperative evaluation of children with drug-resistant epilepsy. *Childs Nerv Syst* 2006;22:810–20.
12. da Silva EA, Chugani DC, Muzik O, Chugani HT. Identification of frontal lobe epileptic foci in children using positron emission tomography. *Epilepsia* 1997;38:1198–208.
13. Gaillard WD, White S, Malow B, Flamini R, Weinstein S, Sato S, et al. FDG-PET in children and adolescents with partial seizures: role in epilepsy surgery evaluation. *Epilepsy Res* 1995; 20:77–84.
14. Juhász C, Chugani DC, Muzik O, Shah A, Asano E, Mangner TJ, et al. Alpha-methyl-³H-tryptophan PET detects epileptogenic cortex in children with intractable epilepsy. *Neurology* 2003; 60:960–8.
15. Snead 3rd OC, Chen LS, Mitchell WG, Kongelbeck SR, Raffel C, Gilles FH, et al. Usefulness of ¹⁸F-fluorodeoxyglucose positron emission tomography in pediatric epilepsy surgery. *Pediatr Neurol* 1996;14:98–107.
16. Chugani HT, Phelps ME, Mazziotta JC. Positron emission tomography study of human brain functional development. *Ann Neurol* 1987;22:487–97.
17. Van Laere K, Vonck K, Boon P, Brans B, Vandekerckhove T, Dierckx R, et al. Vagus nerve stimulation in refractory epilepsy: SPECT activation study. *J Nucl Med* 2000;41:1145–54.
18. Van Laere K, Vonck K, Boon P, Versijpt J, Dierckx R. Perfusion SPECT changes after acute and chronic vagus nerve stimulation in relation to prestimulus condition and long-term clinical efficacy. *J Nucl Med* 2002;43:733–44.
19. Dedeurwaerdere S, Cornelissen B, Van Laere K, Vonck K, Achten E, Slegers G, et al. Small animal positron emission tomography during vagus nerve stimulation in rats: a pilot study. *Epilepsy Res* 2005;67:133–41.
20. Nemeroff CB, Mayberg HS, Kahl SE, McNamara J, Frazer A, Henry TR, et al. VNS therapy in treatment-resistant depression: clinical evidence and putative neurobiological mechanisms. *Neuropsychopharmacology* 2006;31:1345–55.
21. Hopkins DA, Holstege G. Amygdaloid projections to the mesencephalon, pons and medulla oblongata in the cat. *Exp Brain Res* 1978;32:529–47.
22. Ito S, Craig AD. Vagal-evoked activity in the parafascicular nucleus of the primate thalamus. *J Neurophysiol* 2005;94: 2976–82.
23. Ricardo JA, Koh ET. Anatomical evidence of direct projections from the nucleus of the solitary tract to the hypothalamus, amygdala, and other forebrain structures in the rat. *Brain Res* 1978;153:1–26.
24. Crystal GJ, Zhou X, Alam S, Piotrowski A, Hu G. Lack of role for nitric oxide in cholinergic modulation of myocardial contractility *in vivo*. *Am J Physiol Heart Circ Physiol* 2001;281: H198–206.
25. Chapotot F, Gronfier C, Jouny C, Muzet A, Brandenberger G. Cortisol secretion is related to electroencephalographic alertness in human subjects during daytime wakefulness. *J Clin Endocrinol Metab* 1998;83:4263–8.
26. Marroso F, Santoni F, Puligheddu M, Barberini L, Maleci A, Ennas F, et al. Increase in 20–50 Hz (gamma frequencies) power spectrum and synchronization after chronic vagal nerve stimulation. *Clin Neurophysiol* 2005;116:2026–36.